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Abstract

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Epithelial Basement Membrane Dystrophy

A Literature Review

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May 1986

Epithelial basement membrane dystrophy is a category of superficial keratopathies that include microcystic dystrophy, fingerprint/bleb dystrophy, and associated recurrent erosion syndrome. With adult onset and involving only the epitheluim and its basement membrane, classification as a dystrophy was based on early observation that the nonvascular bilateral central changes were unassociated with prior inflammation or systemic disease. However, it is unknown whether etiology is genetic or degeneratory in nature and due to the high prevelance, genetic analysis is very complex.

Microcystic dystrophy was first recognized after five patients with dot-like opacities wre studied and found to have intraepithelial microcysts lying posterior to a thick midepithelial anomalous basement membrane [9]. Subtle irregular gray map areas were considered to be associated with the microcysts and thought to correspond to the aberrant basement membrane[19].

The greatly diminished hemidesmosomal attachments of epithelium to this insinuated basement membrane suggested that microcystic dystrophy and recurrent

epithelial erosion syndrome were related[27,28]. Demonstration of an abnormal layer anterior to Bowman's layer in fingerprint dystrophy and the observation of a similar layer in microcystic dystrophy was first made in 1965[18] and later the association between fingerprint lines and dot opacities was confirmed[20,28,7]. The fingerlike protrusions into the epithelium contain a fine fibrillogranular material inside the extensions of thickened basement membrane.

This same fibrillogranular material is deposited as subepithelial sheets in bleb dystrophy[11]. Ultrastructural analysis indicates the clinical appearance correlates to the spectrum of epithelial changes possible, cumulatively known as epithelial basement membrane dystrophy.

The disease is the most common corneal dystrophy. Once considered rare, prevalence reports now consider half the adult population to have some epithelial basement membrane changes[30]. Usually asymptomatic, visual acuity reduction and erosion symptomology are not uncommon. Visual acuity may be decreased when superficial changes are on the visual axis and of sufficient degree to cause diffraction and irregular

astigmatism. Rarely is the reduction more that two lines of a Snellen chart. Most cases are bilateral, however unilateral corneal involvement is also possible. All changes are central, no limbal involvement has ever been noted.

The subepithelial location of the amorphous material deposition may compromise the efficacy of the epithelial anchoring system leading to erosion episodes. Depending on the integrity of the hemidesmosomal system and the extent of disruption of the anchoring fibrils, epithelial erosion symptomology may range from foreign body sensation to debilitating pain. Erosions are more likely to occur when there are multiple manifestations over large corneal areas. Due to basal epithelial mitotic activity, all effects are transient. Size, shape, and location changing over time producing a relatively benign pathological course. Biomicroscopic appearance of irregular gray patchs with sharp margins (maps), distinct gray-white microcysts (dots), fine concentric refractile lines (fingerprints), small transluscent spots (blebs), rows of blebs along the lines of the anterior corneal mosaic (nets), and gray "smudgy" zones of epithelial erosion

are the visible characteristics of the disease. All combinations of morphologies are possible. Map areas are seen most frequently and are the most common to be found alone. Special slit lamp techniques are required for viewing the subtle changes. Clinical management is directed at the reestablishment of the epithelium to basement membrane connection after an erosive episode, prevention of erosion recurrence, and relief of visual symptoms if warranted.

Map-like or geographic epithelial changes are the essential biomicroscopic feature in microcystic dystrophy because they are often present without microcysts but microcysts are rarely seen without maps[22,12]. The usual coexistence of dots and maps lead to the conclusion that they are variants of the same condition[18,28]. Bietti's lacunar dystrophy is apparently the same disorder[12]. Map areas correlate to a very thick basement membrane extension into the epithelium as multilaminar, 2-6 micron thick collagen sheets described by Cogan[9]. The aberrant basement membrane at the midepithelial level is continuous with the more superficial lamina of the two subepithelial layers and has a similar structure[10,24]. A

misdirection of basal cell secretion may explain the insinuation.

The gray areas become gradually less visible as one moves away from the sharp margins, presumably indicating the edge of the sheets. The raised epithelium produces a thinning of the tear film, most markedly over the map margins. Epithelial cells adjacent to the abnormal basement membrane have no discernible hemidesmosomes and do not resemble basal cells[9,32]. The map designs may cover up to several square millimeters of cornea making them the most potentially harmful erosion precursor.

Production of a thick multilaminar baement membrane, without map-like morphology, is a nonspecific end result of epithelial basal cell activity also seen in Meesman's dystrophy, Fuch's combined, and in female carriers of Fabry's disease[24]. Age related thickening of basement membrane in multilaminar form appears to be a normal function[1].

Intraepithelial microcysts correlate to the small discrete dots seen clinically. Located posterior to the midepithelial aberrant basement membrane, they are up to 1.0mm in size and of various shapes. They are

sometimes referred to as pseudomicrocysts because they have no true lining of their own. The borders are made up of the walls of the adjacent cells which flatten and fuse together to isolate and form the microcysts[5]. The microcysts usually pass through the midepithelial lamina to discharge their contents into the tear film, producing a punctate erosion.

The degeneration process of an epithelial cell becoming a vacuolized and liquified microcyst has been theorized to be based on the mechanical inhibition of the desquamating basal cells by the midepithelial lamina [10,24]and the altered cellular fluid mechanics resulting in a hydropic degeneration sequence of cytoplasmic pallor, acantholysis, cell shrinkage, and microcyst formation[26,12]. The cytoplasmic debris, PAS-positive, and pyknotic nuclei is all that remain[32].

The inhibitory barrier theory of microcyst formation suggests that the trapped basal cells undergo the normal changes designed to make them surface squamous cells but the prevention of forward migration leads to their programmed death and degeneration. This appears valid when considering that microcysts present with maps are found almost exclusively at the margins

of the maps. However, the presence of a barrier to mitotic transport is not a feature of fingerprint dystrophy and other conditions in which microcysts occur. The two theories may be interrelated in that desquamation into an enclosed space may lead to the edematous degeneration process but obviously other factors are involved in these other disorders.

The fine refractile fingerprint lines seen clinically correspond to intraepithelial extensions of basement membrane ensheathing a fibrillogranular material. This material is made of fibrils approximately 17 nm in diameter and granules aproximately 8 nm in diameter with the exact nature of the matrix remaining unknown[3]. The fibrillogranular material is apparently bilaminant and continuous with a subepithelial seam which may explain the erosive tendency of the epithium in the area[3,15]. The processes of the straie may appear to dichotomously branch but are usually grouped into concentric parallel lines occasionly forming a whorl pattern. When present with a stromal scar, the lines will radiate from it, although the scar is not thought to be a precursor[13]. Each line measures 6-14 microns wide and .25-3.0 mm

long[7]. The ends of the processes are the sites of active polymerization suggesting they act as the growing tips[3]. Epithelial cells adjacent to the intraepithelial basement menbrane are apparently normal with adequate hemidesmosomal systems[3,11].

Fingerprint lines were first thought to be due to a previous injury to Bowman's layer[13]. The observation of the arrangement of basal cells coming together base to base within the epithium prompted the theory that a preceding epithilial looseness or unnoticed abrasion respectively caused attenuation of the looseness allowing the cells to come together or overactive migration during healing resulted in the arrangement[24]. The true pathogenesis is unknown. Similar superficial lines have been noted in bullous keratopathy[17,13,10], herpes simplex keratopathy[2], and late Fuch's dystrophy[17]. Solitary lines are morphologically indistinguishable from fingerprint lines except that they are randomly distributed and not grouped together. Superior marginal lines are common in postoperative aphakic eyes due to an edematous response which subsides over time with no erosive symptoms. Mare's tail lines appear parallel but bunch together at one

end. Tram lines are long faint vertical lines that appear in individuals over age 50. All these straited elevations of epithelium produce the tear film thinning and negative staining characteristic.

Bleb appearance is a common concommitant with fingerprints. Bleb dystrophy is characterized by very small clear spots with a pebbled glass appearance. These spots correspond to focal indentations of the basal epithelium by the subepithelial sheets of fibrillogranular material[11]. No deformation of superficial layers occur and no tear film defect is noted.

Blebs are unrelated to the dots in microcystic dystrophy. Adjacent basal epithelial cells are normal in appearance and hemidesmosomal connections[11]. The subepithelial location of the deposition is believed to be responsible for erosive symptomology. Bleb dystrophy was noted in 28% of all patients with recurrent erosion syndrome in a study by Brown and Bron[6]. When present with microcystic dystrophy, bleb dystrophy is thought to be an important precursor to defective epithelial adherence[11]. Rows of blebs may produce a pattern called nets. The blebs in this

configuration follow the lines of the anterior corneal mosaic[4,26,7].

The variations of epithelial basement membrane dystrophy are considered the most common cause of recurrent epithelial erosion[31]. Approximately half of the patients with recurrent erosion syndrome display epithelial basement dystrophy[29]. Clinical and histopathological findings are distinct from other causes of ulceration[6]. The usual site of recurrance is very localized in contrast to traumatic abrasions. Hemidesmosomal loss, subepithelial fluid accumulation and breakdown of anchoring fibrils form the recurrent erosion complex. The abnormal epithelial changes of the dystrophy are visible between attacks. With repeated erosion episodes poor epithelial orientation, misdirected secretory activity, and further modification of the adhesion system occur[15].

Erosions begin as acute ocular pain usually upon awakening. Epiphora, photophobia, and perilimbal injection accompany the blurred vision. The defected epithelium, present as a redundant epithelial tag, is often so loose the removal peels off a large sheet of epithelium. During the first day of healing, the

disrupted epithelium appears gray, edematous, and studded with white cysts that are readily stainable[29,27]. The presence of a Hudson-Stahli line in the close proximity of the erosion site has led to a postulation that the two have a similar pathogenesis or the Hudson-Stahli line is a causative factor in recurrency[31]. Spontaneous recurrence of apparently healed erosion sites are common and plague the patient with low grade foreign body sensation that occasionally erupts into a debilitating defect. Development of an adequate adhesion system may take several months to several years with erosions becoming less frequent as the epithelial connections become more secure. Gradual disappearance of the erosions occur while the dystrophic morphologies remain.

Description of epithelial basement membrane changes has been a relatvely recent event due to the diagnostic challenge of identifying the subtle morphology. All patterns are easily missed without a methodical search of the cornea with special biomicroscopic techniques. Differential diagnosis requires these techniques because the appearance

without other gross abnormalities is considered highly characteristic of the disease.

Map areas require a broad tangential beam to pick up the irregular geographic patch. The gray area may resemble pseudoexfoliation of the lens in appearance[28]. Fingerprints, dots, and blebs are most easily visible with dilated retroillumination off the fundus. Iris retroillumination does not ellicit the patterns as readily. Focusing on the tear film allows discrimination between the lesions and the moving tear film debris. The opaque nature of the microcysts make them easily discernible from the transluscent blebs. As in all elevations of the corneal surface, map margins and fingerprint straie produces a rapid break up of tear film visible with flourescein as negative staining.

A flourescein pattern termed "corneal valance" has been described to pick up the subtle elevations[25]. A horizontal scalloped line across the top third of the cornea was found to correspond to map and fingerprint lines, some of which were not discernible otherwise. It is unknown why some cases of the dystrophy displayed this stable line across the top third of the cornea, in

addition to or instead of the usual random distribution of basement membrane changes.

After age 20, basement membrane thickens by reduplication and this mechanism may be implicated in some of the changes by the disruption of the anchoring fibrils[1]. Most corneal opacities appearing after age 40, like corneal arcus and posterior crocadile shagren, are primary degenerations[14].

No relationship has been found between the epithelial patterns and particular occupations, environmental conditions, medical problems, or medicines. Tear function is unrelated to epithelial integrity and lesion severity is not a function of increasing age[22]. Familial studies have implicated an autosomal dominant inheritance pattern with variable penetrance[21] but the current estimated prevalence rate was unknown at that time.

Basement membrane alteration by traumatic, toxic, allergic, or neurogenic insult may resemble the characteristic abnormalities seen in the dystrophy. Basement membrane changes similar to map, dot, and fingerprint patterns were found as early as two weeks and as late as twelve months following radial

keratotomy[23]. These were clinically indistinguishable from the dystrophic lesions with map patterns seen most frequently. No erosive episodes were noted and the transient changes were not usually visually significant.

Conventional methods of treatment have included hyperosmotic agents, lubricants, topical steroids, debridement, superficial keratectomy, and therapeutic contact lenses. No randomized trial of these treatments has been conducted and the often self resolving nature of this disease has made it difficult to attribute healing to a therapeutic effect or to the usual fluctuation of the disease. Removal of the effected epithelium has been theorized to be therapeutically effective[18,32] but clinical evidence of long term relief of symptoms is recent[15,8]. After superficial keratectomy, no residual basement membrane exists thereby forcing the basal cells to develop entirely new basement membrane complexes instead of trying to secure to a defective anchoring system. Most of the new epithelial areas appear clear of the morphological changes and erosions do not reoccur.

Presence of a redundant epithelial flap indicates the need for debridement. In contrast to superficial keratectomy, debridement does not remove the defective basement membrane and erosion may reoccur. Debridement may effect a cure without microcyst recurrence but the map like changes can persist and vision is not always improved[5]. After debridement, installation of a cycloplegic and antibiotic followed by bilateral patching allows reepithelialization in 24-48 hours[29].

Steroid therapy for this disorder is ineffective[28]. During acute discomfort from erosion or vision interference the use of hyperosmotic agents to decrease epithelial edema and reduce the chances of eyelid adhesion has been proven effective[31,16,29,6,28]. The most commonly used hypertonic agent is sodium chloride. A 5% solution used 3-4 times daily has been shown to sufficiently dehydrate the cornea to aid vision and prevent recurrent erosion in most patients[29,16]. No deliterious effects of this treatment for this disease has been reported.

The use of loose fitting soft contact lenses for patching of recurrent ulcerative areas has been theorized to be effective but induced complications

include serious corneal infection and neovascularization. These manifestations are caused by the excessive time the lens is on the eye, commonly 3 to 6 months, and may effect permenant changes that are more serious than the recurrent erosion or visual blur. Subsequent antibiotic therapy is sometimes needed. Care must be taken in the removal of the lens at the end of the term to prevent a reulceration. Contact lenses for therapeutic use should be restricted to severely symptomatic patients in which close follow-up care can be guaranteed31.

When the patient's ability to function is inhibited a therapeutic regime to minimize discomfort, erosive frequency, and asthenopia should be implemented with topical medication as the probable method of choice.

Summary

Map, dot, fingerprint, and bleb patterns seen in epithelial basement membrane dystrophy are composed of consistent histopathological features of (1) an abnormal epithelium containing intraepithelial microcysts, (2) a thickened multilaminant basement membrane insinuated in the epithelium, and (3) an

unknown fibrillogranular protein deposited between the epithelial basement membrane and Bowman's layer. A misdirection of basal cell activity apparently overproduces the basement membrane material.

With disease onset after age 30, it is unknown whether the changes are an age dependent degeneration or truly dystrophic in origin. Regarded as benign, the disease may be asymptomatic, lead to minor visual symptoms, or cause recurrent erosion syndrome. Presence of the distinct superficial patterns with no ocular or systemic antecedents is the basis for differential diagnosis.

Recognition of this disease as the often underlying cause of recurrent erosions will protect the patient from inappropriate therapy. Sodium chloride solution acting as a hypertonic agent to dehydrate the corneal epithelium is very effective in eleviating blur complaints and erosion recurrency. Superficial Keratectomy is effective when medical treatment fails. The spectrum of responses in this primary corneal disorder is highly prevalent in the adult population and therefore demands eye care practitioner expertise in diagnosis and treatment.

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